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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,849	03/30/2004	Todd Zankel	30610/40037	3684

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EXAMINER
KOLKER, DANIEL E

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,849	ZANKEL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19,21,22 and 58-62* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19,21,58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 21 September 2007 have been entered. Claims 1 – 16, 20, and 23 – 57 are canceled; claims 17 – 19, 21 – 22, and 58 – 62 are pending.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 September 2007 has been entered.

Election/Restrictions

3. Claim 22 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 21 June 2006.

4. Claims 17 – 19, 21, and 58 – 62 are under examination.

Withdrawn Rejections and Objections

5. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection under 35 USC 102(a) over Beliveau (WO 03/009815) is withdrawn as the claims are now limited to administration of agents conjugated to a fragment of SEQ ID NO:1 at least 80% identical to residues 221 – 323. The claims no longer encompass administration of conjugates comprising full-length RAP.

B. The rejection under 35 USC 102(e) over Beliveau (2003/0129186) is withdrawn. The disclosure is identical to that of Beliveau WO 03/009815 and thus the reasons set forth in the preceding paragraph also apply here.

C. The rejections under 35 USC 103(a) are withdrawn in light of the amendments. The rejections had relied on the references by Beliveau, which are not prior art against the instant claims as described above. The remaining references cited in the rejection fail to render obvious the invention.

D. The provisional obviousness-type double-patenting rejection is withdrawn in light of the terminal disclaimer filed 21 September 2007.

E. The concerns about inventorship are withdrawn in light of the remarks filed 21 September 2007. At p. 6 of the remarks applicant's representative stated that co-pending application 11/202566 is currently commonly assigned with the instant application, and that the two applications were owned by the same entity at the time of invention.

F. The objection to claims 17 – 19 for failing to recite sequence identifiers is withdrawn in light of the amendments.

G. The rejection under 35 USC 102(b) over Lenting is withdrawn in light of the amendments as the claims are now limited to administration of agents conjugated to a fragment of SEQ ID NO:1 at least 80% identical to residues 221 – 323. The claims no longer encompass administration of conjugates comprising full-length RAP.

New Rejections and Objections

Claim Objections

6. Claim 17 is objected to because of the following informalities: it recites the abbreviation "RAP" without first defining the term. It is suggested applicant amend claim 15 to recite "conjugated to receptor associated protein (RAP)".

Furthermore, to reflect more conventional claim language, it is suggested that applicant delete the word "active" from claims 17 and 18, as it is not clear what activity the agent should have. Applicant may consider amending the claims to recite "a diagnostic or therapeutic agent". Support for this limitation can be found and p. 5 final paragraph of the specification as filed. Furthermore, amending claims 17 and 18 in this manner would provide proper antecedent basis for "the therapeutic agent" recited in claims 61 - 62.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17 – 19, 21, and 58 – 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardridge (2002. Nature Reviews Drug Discovery 1:131 – 139) in view of Fillebeen (1999. Journal of Biological Chemistry 274:7011 – 7017, cited as reference C12 on the IDS filed 18 June 2004), Neels (1999, Journal of Biological Chemistry 274:31305 – 31311, cited as reference C85 on the IDS filed 5 March 2007), and Saenko (WO 00/71714, cited in office action mailed 9 July 2007).

Pardidge teaches chimeric proteins are useful for treatment of many disorders when it is necessary to deliver a therapeutic compound across the blood-brain barrier (BBB), and teaches that use of a vehicle will enhance drug delivery across the BBB. In particular, the reference teaches administration of a conjugate (which is on point to claims 17 – 19) comprising a targeting vehicle and a neurotrophin is suitable for neuroprotection after ischemia (i.e., stroke), and thus is on point to claims 17 – 19, 21, and 59 (see p. 134, second column). Pardridge discusses the importance of treating humans (see for example p. 134 second column, which clearly discusses the effects of stroke in humans), and thus is on point to claims 58 – 59. Neurotrophins are active agents, and thus the reference is on point to claims 17 – 19; additionally several neurotrophins are recited in claim 61 and encompassed by claims 58 – 60. The reference teaches that many different drug delivery vehicles can be used, including *receptor mediated transcytosis*, which is on point to claims 17 – 19, as well as active-efflux transport, and carrier mediated transport (see p. 132, bottom of second column). Pardridge teaches that BDNF is therapeutic for stroke (p. 134, second column, fourth paragraph), which is on point to claims 61 - 62. However Pardridge does not teach conjugates comprising RAP fragments, as recited in independent claims 17 – 19.

Fillebeen teaches that the BBB is comprised of endothelial cells which form a tight barrier and exclude most solutes. However, the cells that make up the BBB have specific

pp. 7011 - 7012). Fillebeen teaches experiments in which an *in vitro* model of the BBB (bovine brain capillary endothelial cells, BBCEC) was used to determine whether or not lactoferrin (an iron-binding glycoprotein, see p. 7011 first sentence) is brought across the BBB and if so what receptor brings it across the BBB. The reference also teaches that lactoferrin is transported across the BBB in the *in vitro* model (see p. 7013, second column, section entitled "Apical to Basolateral transport of bLf acoss BBCEC Monolayers"). On p. 7016, the reference also teaches that the transcytosis is inhibited by including receptor associated protein (RAP) in the assay, and that RAP binds to and inhibits the actions of low-density lipoprotein receptor (also called LRP). Fillebeen is thus on point to delivery of RAP across the BBB, which is relevant to independent claims 17 – 19. Fillebeen concludes that the experiments indicate that LRP is responsible for the transcytosis of the ligand across the BBB. However while Fillebeen teaches that RAP binds LRP and that LRP mediates transcytosis, the reference does not explicitly teach administration of conjugates comprising RAP for increasing transport across the BBB and does not teach conjugates comprising RAP fragments, as recited in independent claims 17 – 19.

Neels teaches that LRP receptor has four ligand-binding clusters, and that RAP binds to clusters II – IV of LRP (see data summarized in Table 1). Neels also teaches that LRP binds to and internalizes a number of ligands, which are structurally diverse, including apoliporproteins, lipases, proteinases, proteinase-inhibitor complexes, lactoferrin, and an endotoxin, amongst others (see p. 31305, top of second column). Given the diversity of ligands that Neels teaches are both bound *and* internalized by LRP, it is clear that the structures of the ligands are crucial for internalization. Those molecules which have structural elements which permit them to bind to LRP will all be expected to be internalized. While all the data from the experiments reported by Neels are on point to binding and do not mention internalization, given that Neels teaches that the receptor was well-known to bind and internalize a very diverse set of ligands, an artisan of ordinary skill would, upon reading the reference, clearly understand that those ligands which bind are internalized. However Neels does not teach administration of conjugates comprising RAP for increasing transport across the BBB and does not teach conjugates comprising RAP fragments, as recited in independent claims 17 – 19.

Saenko teaches RAP fragments which bind to LRP. See for example p. 29 first paragraph. Saenko teaches that residues 203 – 319 of RAP constitute the receptor-binding region of RAP; See p. 30 first complete paragraph. This fragment is more than 80% identical to residues 221 – 323 of SEQ ID NO:1. It is within the scope of fragments recited in claims 17 –

residues 221 – 323 of SEQ ID NO:1. It is within the scope of fragments recited in claims 17 – 19, and is evidenced to bind the receptor. However Saenko does not teach administration of conjugates comprising this fragment to subjects.

It would have been obvious to one of ordinary skill in the art to conjugate a diagnostic or therapeutic agent, such as BDNF, to a RAP fragment at least 80% identical to residues 221-323 of RAP, and administer this compound to patients in order to increase the transport of the agents across the BBB, i.e. for therapy for stroke. This motivation comes directly from the prior art references themselves. Pardridge teaches that this method (conjugating agents to transport vehicles) is useful for increasing transport of the agents across the BBB and also teaches that BDNF should be used to treat stroke in humans; Fillebeen teaches that RAP binds to LRP receptor and that this receptor is transports molecules across the BBB; Neels teaches that those agents (such as RAP) which bind to LRP are expected to be internalized, which of course is a necessary step in the LRP-mediated transcytosis taught by Fillebeen. Finally, Saenko provides guidance for selecting the specific RAP fragment (residues 203 – 319) which is within the scope of the fragments recited in claims 17 – 19, as the LRP-binding region. While none of the references specifically mention the megalin-binding properties of this fragment, it appears to be provided. Saenko explicitly teaches that residues 203 – 319 are the receptor binding region of the protein (p. 30), and states that LRP is the receptor to be bound by the RAP fragments. Additionally, it is reasonable that those regions which bind LRP will also bind LRP2 (which is a synonym for megalin; see instant specification p. 34 line 21), given the high structural and functional homology between the two. Finally, it is noted that when the prior art teaches the same structures recited in a claim, it is reasonable to infer that inherent properties are necessarily present; see MPEP § 2112(III) and §2112.01(I). The burden is on applicant to show that the recited property is not present in the prior art; see MPEP § 2112(V).

Allowable Subject Matter

8. The prior art does not teach or suggest administration of conjugates consisting of residues 221 – 323 of SEQ ID NO:1 and a therapeutic agent.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner

Daniel E. Kolker, Ph.D.
December 13, 2007